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PREMENSTRUAL DISORDERS

Interdisciplinary consensus on management of premenstrual disorders in Switzerland

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Abstract

Premenstrual disorders (PMD) can affect women throughout their entire reproductive years. In 2016, an interdisciplinary expert meeting of general gynecologists, gynecological endocrinologists, psychiatrists and psychologists from Switzerland was held to provide an interdisciplinary algorithm on PMD management taking reproductive stages into account. The Swiss PMD algorithm differentiates between primary and secondary PMD care providers incorporating different levels of diagnostic and treatment. Treatment options include cognitive behavioral therapy, alternative therapy, antidepressants, ovulation suppression and diuretics. Treatment choice depends on prevalent PMD symptoms, (reproductive) age, family planning, cardiovascular risk factors, comorbidities, comedication and the woman's preference. Regular follow-ups are mandatory.

Keywords

Algorithm, consensus, diagnostic, interdisciplinary expert meeting, premenstrual dysphoric disorder, premenstrual syndrome, Switzerland, treatment

History

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Introduction

The premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) affects women during their entire reproductive years. As symptoms vary, physicians from different disciplines may be consulted for symptom relief, for example, general practitioners (GP), gynecologists and psychiatrists. In order to facilitate and improve the management of women suffering from PMS/PMDD, an interdisciplinary expert meeting of general gynecologists, gynecological endocrinologists, psychiatrists, psychologists and specialists in phytotherapy from Switzerland was held in April 2016 aiming to provide an algorithm on PMS/PMDD management taking reproductive stages into account.

Premenstrual disorders: definition and epidemiology

The International Society for Premenstrual Disorders (ISPD) has published and updated a consensus paper on premenstrual disorders (PMD) [1–4]. Accordingly, a core PMD can be distinguished from variants of PMDs (Table 1). The core PMD can be further subdivided into (1) predominantly somatic

symptoms, (2) predominantly psychological symptoms or (3) mixed somatic and psychological symptoms. The most frequent psychological symptoms are mood swings, irritability, anxiety and depression. Women with predominantly psychological symptoms may also fulfill the Diagnostic and Statistical Manual (DSM)-5 criteria for PMDD [5] (Table 2). Approximately 30–40% of women report PMS symptoms that require treatment, while 3–8% of women during their reproductive years suffer from PMDD [6]. The duration of symptoms varies from a few days to two weeks per menstrual cycle. Symptoms usually worsen one week before and peak two days before menstruation onset. A symptom-free period generally appears before ovulation [7].

Diagnostic procedures

For optimal treatment planning, the first consultation should cover the following aspects/questions (Table 3), followed by a basic laboratory work-up (preferably 2nd to 5th cycle day, fasting, 8 to 9 am) (Table 4) and systematic symptom assessment. Since PMS and PMDD symptoms are unspecific and overlap with those of various other conditions, a valid and reliable prospective symptom inventory is required to confirm the diagnosis [3]. In particular, PMDD is frequently associated with psychiatric comorbidities such as depression (23%), bipolar disorder (8%) and anxiety (7%) [8], and thus, it is important to ask the patient about any known underlying psychiatric disorders and suicidal ideation. While PMDD may be well differentiated from PMS by applying the DSM-5 PMDD diagnostic criteria (Table 2), the differential diagnostics of PMS are more of a challenge. Several tools are available, but the Daily Record of Severity of Problems (DRSP)

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Table 1. Classification of premenstrual disorders (PMD); adapted from Ref. (26).

Premenstrual disorder category	Characteristics
Core premenstrual disorder (PMD)(PMS, PMDD)	Symptoms occur in ovulatory cycles Symptoms are not specified – they may be somatic and/or psychological Symptoms are absent after menstruation and before ovulation Symptoms recur in the luteal phase Symptoms must be prospectively rated (two cycles minimum) Symptoms must cause significant impairment (work, school, social activities, hobbies, interpersonal activities, distress)
Variants of premenstrual disorders (PMD)	Symptoms of an underlying psychological, somatic or medical disorder significantly worsen premenstrually
Premenstrual exacerbation	Symptoms result from ovarian activity other than those of ovulation
PMD due to nonovulatory ovarian activity (rare)	Symptoms result from exogenous progestogen administration
Progestogen-induced PMD	Symptoms arise from continued ovarian activity even though menstruation has been suppressed
PMD with absent menstruation	

Table 2. DSM-5 Criteria of premenstrual dysphoric disorder (PMDD) (2).

- A. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week postmenses.
- B. ≥ 1 symptom must be present:
 - Marked affective lability (e.g. mood swings, sudden sadness, increased sensitivity to rejection)
 - Marked anger or irritability or increased interpersonal conflicts
 - Marked sense of hopelessness, depressed mood, self-critical thoughts
 - Marked tension, anxiety, feeling on edge
- C. ≥ 1 symptom must be additionally present to reach a total of 5 symptoms when combined with symptoms from criterion B above:
 - Difficulty concentrating
 - Change in appetite, food cravings, overeating
 - Diminished interest in usual activities
 - Easy fatigability, decreased energy
 - Feeling overwhelmed or out of control
 - Breast tenderness, bloating, weight gain or joint/muscles aches
 - Sleeping too much or not sleeping enough
- D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others.
- E. The disturbance is not merely an exacerbation of the symptoms of another disorder or personality disorder (although it may co-occur).
- F. Criterion A should be confirmed by prospective daily ratings during at least 2 symptomatic cycles.
- G. The symptoms are not attributable to the physiological effects of a substance or another medical condition.

Table 3. Basic information necessary for shared decision making on PMD treatment; modified according to Ref. (19,27,28).

- Menstrual history/reproductive stage: frequency, duration, heaviness, pain, regularity, amenorrhea, last menstrual period, pregnancy
- PMD history: age at onset, character, timing, severity, absence of presence after menstruation, symptom-free interval during follicular phase
- Impairment: effect on work, school, social activities, family etc. (at least 3-5 days); level of distress
- Underlying medical problem (psychological, physical, medical) that worsen before menstruation onset
- Suicidal ideation
- Tolerance of previous or ongoing hormonal treatment
- Family planning and willingness to use barrier methods of contraception during treatment
- Attitude towards (unlicensed) PMD treatment options
- History of PMD treatment: efficacy, side effects
- Adherence to medication

Table 4. Basic laboratory work-up (serum).

Endocrine disorder/status	Serum marker
Reproductive stage	Follicle stimulating hormone (FSH), estradiol (E2)
Thyroid disorder	Thyroid stimulating hormone (TSH)
Hyperprolactinemia	Prolactin
Cushing syndrome/M. Addison	Cortisol

form, which has been validated as a prospectively self-administered questionnaire, is the most commonly used at least in English-speaking countries [9]. The DRSP consists of 17 common PMS symptoms, including 11 symptoms from the DSM-5 PMDD diagnostic criteria. However, the DRSP has not been validated in German or French. There are four validated questionnaires available in German: Revised Premenstrual Syndrome Questionnaire (Revidierter Fragebogen zum Prämenstruellen Syndrom (PMS-r)) [10], Premenstrual Symptoms Screening Tool (Screening-Instrument für Prämenstruelle Symptome (SIPS)) [11], Premenstrual Tension Syndrome Self-Rating Scale (PMTS-SR) and Premenstrual Tension Syndrome Observer Scale (PMTS-O) [12] and PMS Symptom Diary [13]. The PMS-r consists of 30 items that are each rated on a four-point scale from 0 (none) to 3 (severe). Two versions are available assessing either PMS symptoms in general or current symptoms. The SIPS consists of 14 items that are also each rated on a four-point scale from 0 (none) to 3 (severe). The PMTS-SR consists of 36 items and the PMTS-O of 10 items that are either rated on a two-

point scale (yes/no) (PMTS-SR) or on a five-point scale from 0 (none) to 4 (severe) (PMTS-O), respectively. In addition, current mood situation is assessed by a visual analog scale (scale 0–10) consisting of four items. Regardless of the questionnaire applied, the minimum length of recording should be two consecutive cycles [3]. The unsolved issue of all questionnaires is that there are no cutoff values that define PMS. In contrast, in research, the strict PMS criteria of the National Institute of Health (NIH) need to be fulfilled, that is an at least 30%-increase of PMS symptoms from the follicular (day 5 to 10 of the menstrual cycle) to the luteal phase (6 days before menses) [14]. In contrast, PMDD is clearly defined by DSM-5 criteria [5].

Overview of treatment options

Treatment options comprise cognitive behavioral therapy (especially for PMDD), alternative treatments, psychotropic agents, hormone-based treatments, diuretics and surgery. Importantly, in

Table 5. Alternative treatments (selection); modified according to Ref. (23).

Micronutrient	Dosage
Calcium	1200 mg/day; continuous
Vitamin E	150–600 IU/day; continuous
Vitamin B6 (pyridoxine)	50–100 mg/day; continuous
Magnesium	200–500 mg/day; continuous
Myo-inositol	12 g/day powder; continuous
Herbal therapy	Dosage
<i>Vitex agnus-castus</i> L., fructus (chasteberry)	20 mg/day*; continuous
<i>Hypericum perforatum</i> L., herba (St John's wort)	900 mg/day*; continuous
<i>Oenothera biennis</i> L., oleum (evening primrose oil)	1–6 g/day; continuous
<i>Crocus sativus</i> L. (Saffron)	30 mg/day*; continuous
<i>Ginkgo biloba</i> L., folium	120–160 mg/day*; luteal phase

*dry extract.

Switzerland, except for chasteberry (*Vitex agnus-castus* L.) and progesterone none of the following therapeutic options is approved for PMD treatment.

Alternative treatments

Alternative therapies include diet, exercise, micronutrients (calcium, pyridoxine, magnesium, vitamin E, myo-inositol), herbal pharmacological treatments (chasteberry (*Vitex agnus-castus* L.), St John's wort (*Hypericum perforatum* L.), evening primrose oil (*Oenothera biennis* L.), saffron (*Crocus sativus* L.), *Ginkgo biloba* L., and non-pharmacological treatments such as cognitive-behaviour therapy and acupuncture. Importantly, herbal treatments may be approved as food supplements or drugs registered by Swissmedic in which case they respond to efficacy, safety and production control criteria. The strongest evidence for efficacy of alternative treatments for PMD exists for calcium, chasteberry (*Vitex agnus-castus* L.) and cognitive-behaviour therapy (Table 5) [3,15]. A systematic review found chasteberry extracts to be superior to placebo, pyridoxine and magnesium oxide in women with PMS [16]. In women with PMDD, one study reported chasteberry to be equivalent to fluoxetine [17], while in the other, fluoxetine outperformed chasteberry [18]. *Vitex agnus-castus* was effective in reducing both, somatic and mental symptoms [16]. The overall response of PMD patients to *Vitex agnus-castus* L. ranged between 52–81% [16,19]. A treatment period of at least 3 month is recommended [20,21]. However, it should be kept in mind, that chasteberry is a dopaminergic agonist [21] and might thus interfere with antipsychotics (no studies yet).

Psychotropic agents

Psychotropic agents comprise antidepressants and anxiolytics (Table 6) [1,2,3,15,22]. Antidepressants can be applied continuously or during the luteal phase only (start: 14 days before the expected onset of menstrual bleeding; stop: onset of menstrual bleeding or a few days later). The overall response of PMD patients to selective serotonin reuptake inhibitors (SSRI) ranges between 50–90% [23,24]. The beneficial effect can be expected within 48 h of treatment initiation. While continuous and intermittent SSRI treatments are equally effective at reducing irritability and mood swings, continuous SSRI treatment is more effective in reducing depressed mood and somatic symptoms [25,26]. If there is insufficient response in the first treatment cycle, the dose might be increased in the next cycle or the type of

Table 6. Psychotropic treatment PMD options; modified according to Ref. (23).

Antidepressant	Dosage
Selective serotonin reuptake inhibitors (SSRI)	
• Sertraline	50–150 mg/day; continuous or luteal phase
• Fluoxetine	10–20 mg/day; continuous or luteal phase
• Escitalopram	10–20 mg/day; continuous or luteal phase
• Paroxetine	12.5–25 mg/day; continuous or luteal phase
• Citalopram	10–30 mg/day; continuous or luteal phase
Selective serotonin norepinephrine reuptake inhibitors (SNRI)	
• Venlafaxine	50–200 mg/day; continuous or luteal phase
• Duloxetine	60 mg/day; continuous
Tricyclic antidepressants	
• Clomipramine	25–75 mg/day; continuous or luteal phase
Anxiolytic medication	Dosage
• Alprazolam (drug dependence!)	0.75 mg/day; luteal phase
• Buspirone	10–40 mg/day; luteal phase

SSRI may be changed. Side effects, such as nausea, insomnia, headache, fatigue, diarrhea and dizziness, are common at SSRI initiation (incidence 15%) but usually abate within a few days of treatment. In contrast, sexual dysfunction such as decreased libido or delayed orgasm may be persistent (incidence 9–30%) but recovers rapidly after SSRI discontinuation. So far, suicide attempts have not been reported in women with PMD using SSRI or SNRI, respectively [27]. Although discontinuation symptoms are rare SSRI dose may be tapered, especially when given on a continuous basis [27]. After discontinuing treatment, about 50% of patients experience a relapse within 6–8 months. But even in women on medication relapse may occur [28]. Combining SSRI with other medications (e.g. association of multiple antidepressants) has not been systematically studied for PMD treatment.

Similar to SSRI, selective serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants and anxiolytics have been shown to improve PMD. However, the body of evidence is much smaller [15].

In women presenting with variant PMD, such as premenstrual exacerbation, of an underlying psychiatric disorder antidepressant therapy should be established in close collaboration with a psychiatrist as in some patients with, for example, prepsychotic disorder, SSRI may aggravate the underlying psychiatric condition. Furthermore, when treating fertile women for core PMD, choosing a SSRI compatible with pregnancy (e.g. sertraline, citalopram) is recommended.

Suppression of ovulation

Ovulation can be suppressed by using combined oral contraceptives (COC), gonadotropin-releasing hormone agonists (GnRH-A), estrogens and danazol (not available anymore in Switzerland) (Table 7). While early studies showed a negative impact of COC on affective symptoms in women suffering from PMD, there are others, especially those containing the progestogen drospirenone and/or with shortened pill-free interval that demonstrated a benefit for affective and somatic symptoms, respectively [3,15,29]. However, as COC increase the risk of venous thromboembolism, adequate counseling is mandatory [30].

GnRH-A downregulate the hypothalamus–pituitary–ovary axis, thereby inducing a pseudo-menopausal state. The response rate in women with PMD has been reported to be 60–75% for both, physical and behavioral symptoms [31]. GnRH-A are

Table 7. Suppression of ovulation for PMD treatment, modified according to Ref. (23,26).

Suppression of ovulation	Dosage; regimen
Combined oral contraceptives (COC) (selection)	<ul style="list-style-type: none"> • 20 mcg ethinylestradiol + 3 mg drospirenone; monophasic 24/4* • 20 mcg ethinylestradiol + 90 mcg levonorgestrel; monophasic continuously • 35 mcg ethinylestradiol + 0.5/1/0.5 mg norethindrone; triphasic 21/7 • 30 mcg ethinylestradiol + 150 mcg desogestrel; monophasic 21/7 • 30 mcg ethinylestradiol + 150 mcg levonorgestrel; monophasic 21/7 • 30/40/30 mcg ethinylestradiol + 50/75/125 mcg levonorgestrel; triphasic 21/7 • 30 mcg ethinylestradiol + 2 mg chlormadinone acetate; monophasic 21/7
Gonadotropin-releasing hormone agonists (GnRH-A)	<ul style="list-style-type: none"> • Leuprolid 3.75 mg i.m./month • Goserelin 3.6 mg s.c./month or 10.8 mg s.c./3 months • Buserelin 3 × 100 mcg/day nasal spray
Transdermal estrogens	<ul style="list-style-type: none"> • Estradiol 2–4 × 100 mcg patches/week (combined with a progestogen for endometrial protection)

mcg: microgram; s.c.: subcutaneous; i.m.: intramuscular.

*Approved by the FDA for treatment of PMDD in women who desire contraception.

usually accompanied by “add-back” menopausal hormone therapy (MHT; estrogens combined with progestogens, tibolone) to avoid estrogen deficiency sequelae such as hot flushes and osteoporosis [3,6]. However, long-term safety data are not available yet. Thus, bone densitometry scans are recommended if GnRH-A (\pm MHT) are applied for more than six months and at least at two-year intervals thereafter or at individual intervals, respectively (cave: might not covered by health insurance). Treatment should be stopped if bone density declines significantly in scans performed one year apart [27].

Transdermal and injectable, but not oral estrogens [32–34] suppress ovulation and significantly improve PMD symptoms compared to placebo. For endometrial protection, a progestogen needs to be combined, for example, dydrogesterone (no centralnervous effect) or a levonorgestrel-containing intrauterine device (Mirena®). The latter has some systemic absorption with highest levels in the first 3–4 months, which may induce symptoms such as depression, tiredness and bloating in about 10% of women with progestogen intolerance [35]. Usually, these symptoms disappear thereafter.

Obviously, surgery with bilateral oophorectomy and hysterectomy remains the last-resort treatment for PMD. The beneficial effect on both mood and physical PMD symptoms has been shown, but only as long as add-back MHT with estrogens (unopposed) is administered. Prior to surgery, the potential effect of oophorectomy should be tested by using GnRH-A [3].

Progestogens

Neither progestins nor progesterone have been proven to be effective in women suffering from PMD and are therefore not generally recommended [1,2,22,27,36]. However, the most recent Cochrane review stated that the (heterogeneous) trials included did not show that progesterone was not an effective treatment for PMS [37].

Diuretics

Spironolactone, an aldosterone receptor antagonist, at 100 mg/day during the luteal phase has been shown to reduce both physical and affective symptoms [38,39]. As spironolactone is a potassium-sparing diuretic, patients should periodically be monitored for hyperkalemia [15].

Swiss algorithm for PMD management

The Swiss algorithm for PMD management seeks to incorporate the structural level of medical care (primary/secondary care) as

well as varying content levels (diagnostics, treatment) depending on the reproductive stage of a woman (reproductive phase, menopausal transition (MT)) [40].

On the hierarchical level (Figure 1), GPs and general gynecologists are responsible for primary PMD care, while gynecological endocrinologists (lead clinician), psychiatrists and psychologists are providers of secondary PMD care. Together with the patient, they form a therapeutic triangle that may be supplemented by for example approved alternative medicine specialists and surgeons if indicated. Primary clinical diagnostics (personal history, prospective symptom assessment) should be performed by the primary PMD care provider. The interdisciplinary expert panel recommends to use the PMS-r either daily or at least twice per menstrual cycle (e.g. during follicular phase (cycle day 5–7) and luteal phase (either 14 days later or 6 days prior to the next menstruation)) during two consecutive cycles. For French-speaking patients, the Calendar of Premenstrual Experiences (COPE) is currently used. Its translation in French has however never been validated.

If first- and second-line treatment (Figures 2 and 3) is not successful, the patient should be referred to a secondary PMD care provider, preferably to a gynecological endocrinologist. A psychiatrist is the preferred secondary PMD care provider if a woman presents with variant PMD with psychiatric co-morbidity. Clinical diagnostics will then be completed by a serum laboratory work-up and eventually by another prospective symptom assessment during two consecutive cycles.

The proposed treatment algorithm distinguishes between women during their reproductive years and women during the MT [40]. Each treatment trial should be documented in the same way as during the diagnostic cycles.

Psychoeducation should be the basis for all following treatment options. For treatment-naïve women in their reproductive years (Figure 2), first-line treatment comprises alternative therapy (at least 2–3 months). In nonresponders or pretreated women, second-line treatment comprises either a 2-month course of COC (if contraception is needed and VTE risks are absent) or antidepressants (SSRI, SNRI) (if no contraception is needed or VTE risks are present) at different dosages and regimens. Patients who start on SSRIs should be offered a follow-up appointment (face to face or phone) 1 week after treatment start in order to assess for increased anxiety [4]. In women seeking to become pregnant, citalopram and sertraline are the preferred SSRI. Tricyclic antidepressants and anxiolytics should only be prescribed by psychiatrists and in women with severe PMDD.

In nonresponders or women with side effects, third-line treatment can be either spironolactone or ovulation suppression

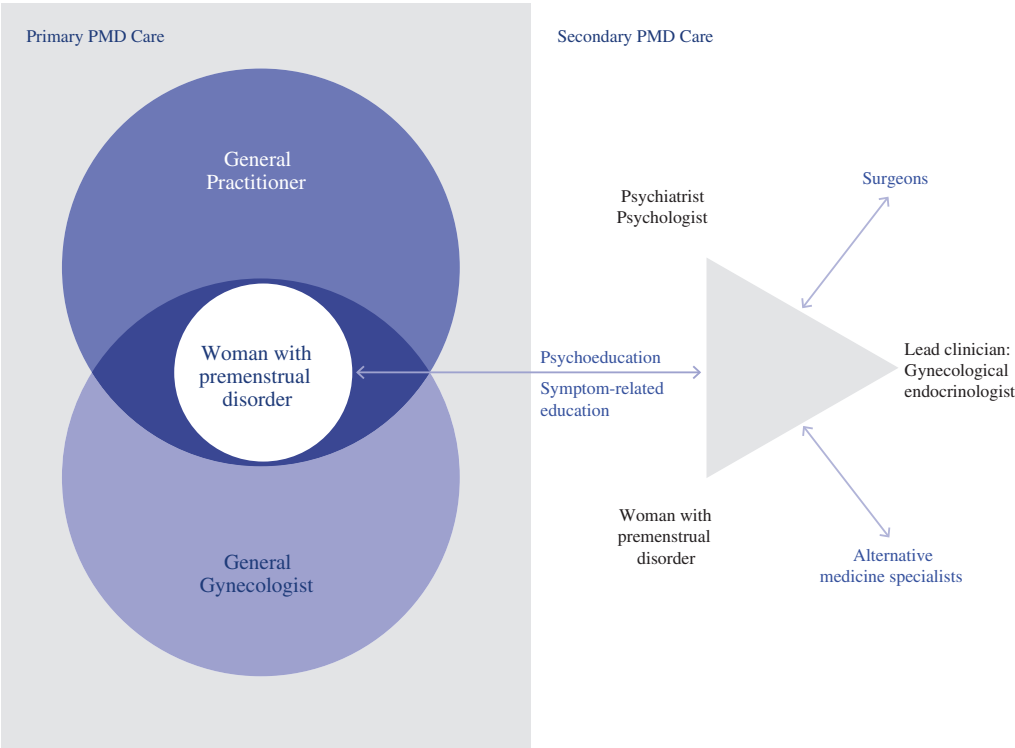


Figure 1. Premenstrual disorder (PMD) health care model.

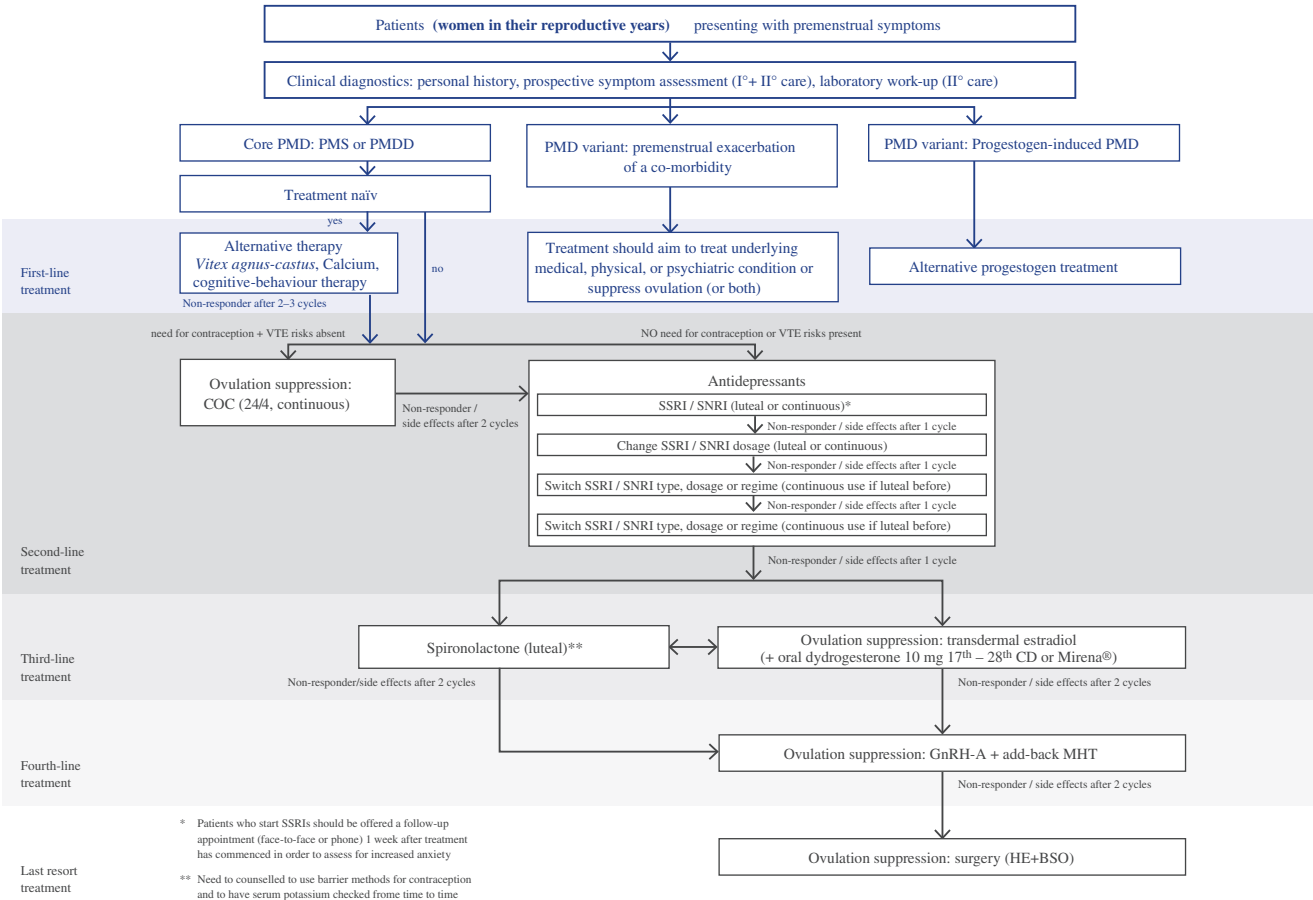


Figure 2. Algorithm on premenstrual disorder (PMD) management for women during their reproductive years.

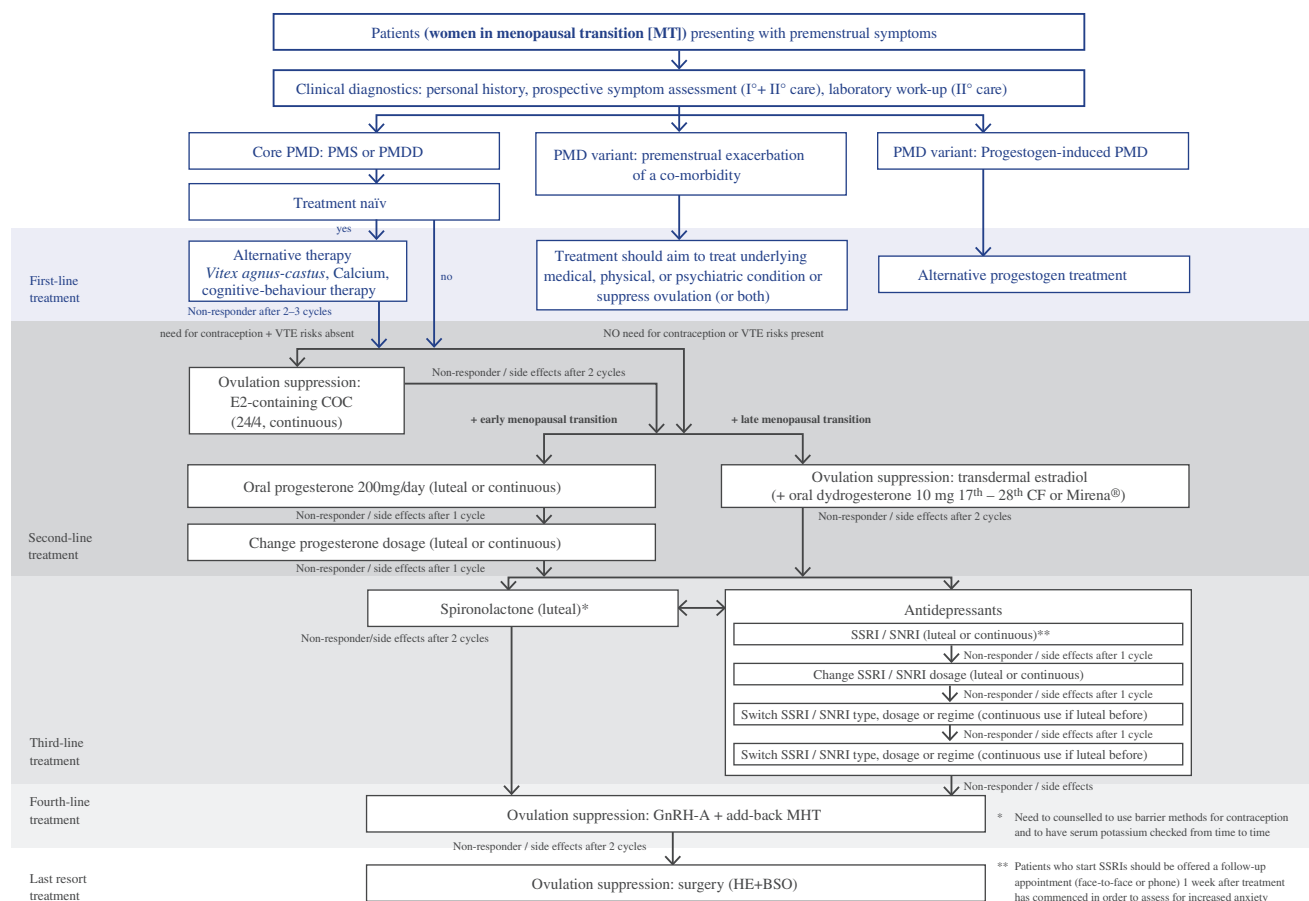


Figure 3. Algorithm on premenstrual disorder (PMD) management for women during the menopausal transition.

by transdermal estrogens combined with a progestogen for endometrial protection. Women choosing spironolactone need to be counseled to use barrier methods for contraception and to have serum potassium checked from time to time.

Women who do not respond to any third-line treatment option may be offered ovulation suppression by GnRH-A combined with add-back MHT (fourth-line treatment). In responders, bone densitometry should be evaluated after six months and at least at two-year interval thereafter or at individual intervals, respectively (might not covered by insurance!). Surgery with hysterectomy and bilateral oophorectomy is the last-resort treatment and not necessary in most cases.

Women suffering from core PMD during their reproductive years should be informed about their increased risk of depression during pregnancy, postpartum and the perimenopause in order to provide easy and fast access to interdisciplinary medical care during hormone-sensitive life stages.

Women during the MT may face a new onset or worsening of premenstrual symptoms. Early MT is characterized by a variation of the menstrual cycle length that exceeds 7 days, more consistently elevated FSH serum levels and a decreased ovarian reserve. Late MT is characterized by irregular and scarce menstrual cycles, more likely low estrogen serum levels and an increased prevalence of common menopausal symptoms [40,41].

Similar to women suffering from PMD during their reproductive life span, treatment-naïve women during the MT (Figure 3) may try alternative therapy as first-line treatment (2–3 months). In nonresponders or pretreated women, second-line treatment comprises either a 2-month course of E2-containing COC (if contraception is needed and VTE risks are absent), oral progesterone (early MT, if no contraception is needed or VTE

risks are present) or ovulation suppression by transdermal estrogens combined with a progestogen for endometrial protection (late MT, if no contraception is needed or VTE risks are present). In nonresponders or women with side effects, further treatment options comprise antidepressants, spironolactone (third-line treatment), GnRH-A combined with add-back MHT (fourth-line treatment) and surgery with hysterectomy and bilateral oophorectomy (last resort treatment). In conclusion, the Swiss algorithm for PMD management is a tool to triage PMD care with regards to reproductive life stage in an interdisciplinary context. Medical care is structured on five treatment levels.

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Declaration of interest

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